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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/773,041	01/31/2001	Ronald M. Evans	033123-005	1754

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EXAMINER	
PAK, MICHAEL D	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/773,041	EVANS ET AL.	
	Examiner	Art Unit	
	Michael Pak	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-15 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Reissue Applications

1. The original patent, or a statement as to loss or inaccessibility of the original patent, must be received before this reissue application can be allowed. See 37 CFR 1.178.

2. Applicant is notified that any subsequent amendment to the specification and/or claims must comply with 37 CFR 1.173(b).

3. Claims 1-15 are pending.

Oath/Declaration

4. The reissue oath/declaration filed with this application is defective because the error which is relied upon to support the reissue application is not an error upon which a reissue can be based. The declaration state that "... Patent No. 4,981,784 may be at least partly inoperative..." However, the declaration must fully declare that the Patent "to be" inoperative. See 37 CFR 1.175(a)(1) and MPEP § 1414.

Specification

5. The disclosure is objected to because of the following informalities. Column 9, lines 25-30 contains an old address of ATCC. It is suggested that an updated address of ATCC be used.

Appropriate correction is required.

6. The references cited in the reissue patents will not be printed automatically. It is suggested that references be cited in the form 1449 as a submission for information disclosure statement if applicant desires the publication of the references and patents relevant to the reissue patent.

Claim Objections

7. Claims 12 and 14 are objected to because of the following informalities. Claims 12 and 14 recite acronyms which are not defined and should be defined by its appropriate terms. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-6, 9, and 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, 9, and 12 recite the term "gene" whose metes and bound are not clear and thus the term is confusing and ambiguous. The term gene encompasses regions of nucleic acid which do not encode proteins such as the regulatory regions whose metes and bounds are not clearly set forth. Claims 2, 3, 5-6, 9 and 13 are dependent on claim 1 or 12 and/or encompass the term.

Claims 2-5 recite dependency on a specific claim limitation of claim such as "method according to claim 1(b)", "method according to claim 1(c)", and "method according to claim 1(c)2" which is confusing and ambiguous because the claims cannot be dependent on a specific claim limitation but rather the whole claim. Claims 6 is dependent on claim 5 and/or encompass the term. Examiner suggests that claim 3 would be clearer if it stated: a method according to claim 1, where the host cell of claim 1(c) is a COS host cell.

Claim 9 recites the limitation " the reporter gene " in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claims 12 and 14 recite acronyms of chimeric receptors whose terms are not clearly defined in the specification and the metes and bounds of which are not clear. Examiner suggests that the full name of the acronym as supported by the specification be used in conjunction with the acronym which provides function and structure to the limitations.

Claims 1-11 and 14-15 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The claims omit steps necessary to fulfill the stated purpose of the preamble of identifying a functional ligand. Claim 1 recite "capable" which does not provide the steps necessary for the method.

9. Claims 1 and 3-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Written description rejection.

Claims 1 and 3-9 are drawn to a method that uses a genus of DNA encoding all receptors with ligand binding and DNA binding domain. However, the specification only discloses a single species of retinoic acid receptor disclosed in Figure 1. The specification does not disclose what structural features, other than the full length sequence of the single species of figure 1, must be retained in order to render a protein as a retinoic acid receptor. The specification fail to disclose what specific functions are considered to be definitive of retinoic acid receptor and what specific structures are critical to their retention. The claims are drawn to a genus that need only be related or retain a function that is "characteristic" of any receptor without a definition of what functions are characteristic and what structures other than the full length sequence of figure 1 are required for said functions. Without said information, the single species

cannot be representative of such a broad genus. *University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398* (*Eli Lilly*) held that a generic claim to human, mammalian or vertebrate protein when only the rat protein sequence was disclosed, did not have written description in the specification. The essential feature of the invention is the single species of DNA encoding the retinoic acid receptor of Figure 1. The specification with a single species does not provide support for the claimed genus because *Eli Lilly* held that one skilled in the art could not envision the structure of the genus of proteins in other species such as human or the genus of mammalian or vertebrate proteins. In the same manner, one skilled in the art cannot envision the genus of any receptors structure and thus the specification does not provide adequate disclosure for the claimed genus.

10. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method using the specific functional receptors cited in claim 2: glucocorticoid receptor, mineralocorticoid receptor, human thyroid receptors alpha and beta, rat throid receptor alpha and retinoic acid receptors alpha and beta, does not reasonably provide enablement for the method of using orphan receptors such as estrogen related receptors hERR1 or hERR2, or method of using the genus of receptors with only the ligand binding and DNA binding domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The first paragraph of § 112 requires that the patent specification enable "those skilled in the art how to make and use the full scope of the claimed invention without `undue experimentation.'" Genentech, Inc. v. Novo Nordisk AIS, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)); see also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). ("[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."). Whether making and using the invention would have required undue experimentation, and thus whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-37, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Likewise, in Amgen Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991), the court affirmed the holding of invalidity of claims to analogs of the EPO gene under § 112 for lack of enablement where applicants had claimed every possible analog of the EPO gene but had disclosed only how to make EPO and a very few analogs. "[D]espite extensive statements in the specification concerning all analogs

of the EPO gene that can be made, there is little enabling disclosure of the particular analogs and how to make them .... There may be many other genetic sequences that code for EPO-type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them." Id., 927 F.2d at 1213-14, 18 USPQ2d at 1027. Claims 1 and 3-9 are too broad to be enabled by a specification that provides only one example of an embodiment of the claimed invention. Here, claims 1 and 3-9 are not limited to DNA encoding any specific retinoic acid receptor (i.e., RAR or RXR) of any specific isotype (e.g., RARα, RARβ or RARy) or isoform (e.g., RARα1 or RARα2) from any particular species (e.g., mammal, amphibian, bird or fish). Claims 2, 10-15 encompass a method of using the specific orphan receptors, estrogen related receptors hERR1 and hERR2 and claims 1 and 3-9 encompass using the a genus of orphan receptors because the claims are drawn to a genus of any receptors with DNA binding and ligand binding domain. The specification only describes one DNA sequence (i.e., phRAROc1) encoding one isoform of one isotype of one protein member of a "gene family" from only one species, i.e., human RARa1.

The amount of direction provided in the specification is limited to isolation and characterization of phRARa1. The specification has identified a range of nucleotides and amino acid which span the DBD and the LBD in hRARa and phRAROc1, but not which nucleotides and amino acids are critical to binding a retinoic acid ligand and a retinoic acid response element. Neither does the specification identify which amino acid and/or nucleic acid subsequences are conserved between either isotypes, e.g., RARα, RARβ or RARY, or between species, e.g., mammals, fish, amphibians or birds. Thus,

the specification provides no evidentiary basis for reasonably predicting how the primary sequence homology correlates to structural/functional homology, The specification does not teach the critical amino acid/nucleic acid sequences necessary to bind retinoic acid and thereby unmasking the DBD of the receptor have not been identified. Even proteins with highly homologous sequences can function very differently for example 3-hemoglobin and its gene in normal individuals and patients with sickle cell anemia. The specification does not teach the identification of a ligand for orphan receptors of estrogen related receptors. Orphan receptors are receptors which are identified by structural relationship but the functional ligand of the receptor is not known. Without the ligand, the function of the receptor requires undue experiementation to determine the lfunction of the receptor.

Furthermore, to the extent that the Southern blot/low stringency hybridization analysis described in the specification might suggest the existence of one or more genes encoding other proteins with closely related properties to hRARα, The specification does not describe the isolation and characterization of these genes or how to make them. Moreover, the fact that other RAR's have been isolated, sequenced and characterized in subsequent publications does not lead to the conclusion that the specification taught how to make them. 24 Gould v. Quiaa, 822 F.2d 1074, 1078, 3 USPQ2d 1302, 1305 (Fed. Cir. 1987) ("A later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling.") Even the specification describes the hap gene identified by Dejean in 1986 and later identified as

being the RAR gene, as giving an "unrelated" pattern under high stringency hybridization analysis.

Assuming arguendo that other DNA sequences were isolated by a low stringency hybridization analysis as described in the specification, whether those DNAs actually encoded retinoic acid receptors or encoded receptors for other ligands appears unpredictable, i.e., a ligand screening assay based on chimeric receptor constructs would have to be performed which would require undue experimentation. As to the state of the art, the modular nature or "domain" organization of nuclear receptor proteins "was first noted in a sequence alignment of the estrogen receptors of different species" by Krust et al. p. 1181, c. 1. Green's paper describes replacing the DBD of an estrogen receptor protein with the DBD of a glucocorticoid receptor to produce a chimeric receptor, p. 851. Green stated that

> [o]ne important consequence of the results reported here is the possibility of creating chimaeras between trans-acting transcriptional regulatory factors that contain sequences homologous to the steroid hormone receptor region C [i.e., DBD] (c. 1, 13).

Thus, the state of the art appears to be evolving, rather than mature.

Therefore, based on the above Wands analysis, a preponderance of the evidence supports a conclusion that one skilled in the art would not have been enabled to make and use the invention of claims 1-15 without undue experimentation.

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Pak, whose telephone number is (571) 272-0879. The examiner can normally be reached on Monday through Friday from 8:30 AM to 2:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871.

The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-0507.

Michael D. Pak

Michael Pak
Primary Patent Examiner
Art Unit 1646
18 March 2003